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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/971,929	10/09/2001	Naoyuki Takano	2185-0577P	2971

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EXAMINER

GUDIBANDE, SATYANARAYAN R

ART UNIT	PAPER NUMBER
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1654

MAIL DATE	DELIVERY MODE
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08/15/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/971,929	Applicant(s) TAKANO ET AL.	
	Examiner SATYANARAYANA R. GUDIBANDE	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5,7,9-14 and 16-21 is/are pending in the application.
- 4a) Of the above claim(s) 3-5,7,16 and 18 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 19 is/are allowed.
- 6) ☒ Claim(s) 1-5,7,9-14 and 16-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of species chitosan trisaccharide and diethylenetriaminepentaacetic acid in the reply filed on 9/26/06 was acknowledged in office action dated 10/30/06.

Examiner searched the elected species chitosan trisaccharide and diethylenetriaminepentaacetic acid found them free of art. Examiner extended the search and found art on serum albumin and diethylenetriaminepentaacetic acid.

Applicant's amendment to claims 1 and 19-21 in the response filed on 4/8/08 has been acknowledged.

Claims 1-5, 7, 9-14 and 16-21 are pending.

Claims 6, 8 and 15 have been canceled.

Claims 3-5, 7, 16 and 18 are withdrawn from further consideration as being drawn to non-elected species.

Claims 1, 2, 9-14, 17 and 19-21 are examined on the merit.

Allowable Subject Matter

Claim 19 contain allowable subject matter, i.e., claim is drawn to the elected species chitosan trisaccharide that has been found to be free of art, but contains other species chitosan tetra- to deca-saccharide.

Any objections and/or rejections made in the previous office action dated 1/8/08 and not specifically mentioned here are considered withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,2, 9-14, 17, 20 and 21 remain rejected under 35 U.S.C. 102(b) as being anticipated by Paik, et al., J. Nucl. Med. 1983, 1158-1163.

In the instant application, applicants claim a process of producing an amide bond that comprises of reacting a compound having an amino group with a polyaminopolycarboxylic acid anhydride in the presence of the polyaminopolycarboxylic acid.

Note: Applicant's arguments have been addressed at the end of the reiteration of the rejection.

Paik, et al., teaches such a method of amide formation. The reference teaches the preparation of DTPA coupled serum albumin antibody. In the process, Paik, et al., affinity-purified antibody (300 µg, 2.0 nmol) was dissolved in 1 ml of 0.1M buffer solution (Hepes buffer at pH 7, phosphate at pH 7, borate at pH 8.6, or bicarbonate at pH 8.2) in a 2.5-ml vial. To the antibody solution was added solid cyclic DTPA anhydride (page 1159, column 2, paragraph 1). However, during the IR (infrared spectroscopy) analysis of the DTPA anhydride, Paik, et al.,

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the IR spectrum showed absorption bands at 1825 and 1780 cm^{-1} , characteristic stretching vibrations for the **anhydride carbonyl group**. The IR spectrum also showed an absorption at 1640 cm^{-1} indicating the presence of a **carboxylate group**. The claim limitation that the presence of both polyaminopolycarboxylic acid anhydride and the presence of the polyaminopolycarboxylic acid in the reaction mixture is met by the fact that the anhydride used in the preparation was a mixture of the anhydride and the free acid as shown by the IR analysis. Therefore, this meets claim limitations of claims 1 and 21. Also, during the DTPA conjugation reaction, the reaction reduced the pH of buffer solution to 4. Due to the hydrolysis of the anhydride that produced four acetic acid molecules (page 1161, column 1, paragraph 1) further affirming the presence of free polyaminocarboxylic acid in the reaction mixture. The reaction was carried out in bicarbonate buffer, pH, 8.2 as mentioned above and hence in basic condition that meets one of the limitations of claim 21.

Response to Arguments

Applicants argue that “not all instantly claimed features are disclosed in the cited reference of Paik, et al., specifically, the claimed processes are different from the disclosed process of Paik et al”.

Applicants state that “they have previously amended claims 1 and 19-21 to recite that the polyaminopolycarboxylic acid anhydride is added to a mixture of the compound having an amino group and the polyaminopolycarboxylic acid, or the compound having an amino group and the polyaminopolycarboxylic acid anhydride are added to the polyaminopolycarboxylic acid.

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In stark contrast, the cited reference clearly fails to teach or suggest such an embodiment. The cited reference teaches that the DTPA anhydride hydrolyzes in the presence of water (page 1158, column 2), with the requisite reaction occurring in the presence of polyaminopolycarboxylic acid due to the presence of hydrolyzed product of the DTPA anhydride being present in the reaction mixture. In other words, any acid which is present is due to its in situ formation”.

As amended, the simultaneous addition of the polyaminopolycarboxylic acid anhydride and polyaminopolycarboxylic acid is not encompassed by the claims. Regardless, Applicants respectfully traverse the Examiner's assertion regarding the presence of 0.1% impurity of unreacted DTPA or hydrolyzed anhydride compounds. The Paik et al. reference does not disclose such impurities. Furthermore, the present application clearly defines polyaminopolycarboxylic acid anhydride. The bicarbonate of the Paik et al. reference is not a polycarboxylic acid. The Examiner asserts that the claim as recited does not imply that the polyaminopolycarboxylic anhydride is derived from the same polyaminopolycarboxylic acid. Applicants have amended the claims to further clarify the invention that "the polyaminopolycarboxylic group of both said acid and said acid anhydride are the same.

With the respect to the Examiner's reliance on Le Chatelier's Principle, Applicants respectfully traverse. The polyaminopolycarboxylic acid cannot easily be converted to its anhydride in the present process. The addition of polyaminopolycarboxylic acid does not favor the formation of polyaminopolycarboxylic acid anhydride in the reaction condition. It cannot properly be said that the addition of polyaminopolycarboxylic acid assists the formation of the desired product. The scheme illustrated on page 8 of the Office Action does not cover the other

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side reactions occurring in the reaction mixture. Other side reactions are present in the reaction mixture, and the real reaction in the mixture is rather complex”.

Applicant's arguments filed 4//8/08 have been fully considered but they are not persuasive.

With regards to applicant's argument that the reference of Paik does not disclose presence of such impurities regarding “Offices's assertion that the presence of 0.1% unreacted DTPA or hydrolyzed anhydride being present along with the cyclicDTPA anhydride" is not persuasive. The reference clearly indicates that Paik, et al., observed a IR resonance for the free carboxyl group. It is true that the resonance can be from the 5th carboxylic group of the cyclic anhydride of DTPA. However, it cannot be attributed to only the unreacted carboxyl group considering the fact that anhydrides are well known for their instability.

In light of current amendment to the instant claims 1 and 20, 21 the statements made with respect Hepes buffer and bicarbonate being the polyaminopolycarboxylic moieties are withdrawn.

With regards to applicant's argument about the Office's reliance on Le Chatelier's principle that “the addition of polyaminopolycarboxylic acid cannot easily be converted to its anhydride and the addition of polyaminopolycarboxylic acid does not favor formation of polyaminopolycarboxylic acid anhydride,” is not persuasive. Because, in the office action, Office clearly stated that “the addition of DTPA to the reaction would **deter the rate of hydrolysis reaction of DTPA anhydride** and hence favor the formation of the product R-DTPA”. The

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office did not state that addition of polyaminopolycarboxylic acid would favor the formation of polyaminopolycarboxylic acid anhydride.

Thus the rejection as stated in the previous office action dated 3/30/07 is appropriate and maintained.

New grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

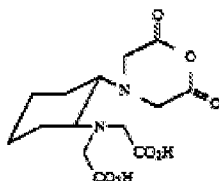
Claims 1, 2, 9-14 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,021,571 issued to Mease, et al.

In the instant application, applicants claim a process of producing an amide bond that comprises of reacting a compound having an amino group with a polyaminopolycarboxylic acid anhydride in the presence of the polyaminopolycarboxylic acid wherein the polyaminopolycarboxylic group of both said acid and said acid anhydride are the same.

Mease, et al., teaches such a method of amide formation. The reference teaches the preparation of CDTA (cyclohexyl EDTA) coupled an albumin antibody (example 11, column 14). In the process, Mease, et al., prepares a conjugate of CDTA and the antibody using CDTAMA (cyclohexyl EDTA monohydrate) in the presence of 0.1 M sodium bicarbonate buffer and the CDTAMA was dissolved in DMSO (reads on instant claims 1, 2 and 12-14). The

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CDTAMA solution was added to the antibody solution. The CDTAMA reagent is a polyaminopolycarboxylic acid since it has two free -COOH functional groups and it is an anhydride since it has a cyclic anhydride moiety as shown in the figure below:



Both the acid and the anhydride are derived from the same polyaminopolycarboxylic acid as required by the instantly amended claims 1 and 21. Since the anhydride and acid belong to the same molecule, addition of the reagent CDTAMA in DMSO reads on the instant claims 1, 11 and 21.

Hence the cited reference of Mease, et al., anticipates the instant invention.

Conclusion

Applicant's amendment to claims 1 and 19-21 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

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CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654